

## **Testimony**

**Before the Committee on Government Reform and Oversight,** 

**Subcommittee on Human Resources United States House of Representatives** 

# Institutional Review Boards: A Time for Reform

Statement of
George Grob
Deputy Inspector General for
Evaluation and Inspections

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For Release on Delivery Expected at 9:30am Thursday June 11, 1998 Good morning. I am George Grob, Deputy Inspector General for Evaluation and Inspections in the U.S. Department of Health and Human Services (HHS). I am pleased to testify at today's hearing on Institutional Review Boards (IRBs). With me is Dr. Mark Yessian, Regional Inspector General for Evaluation and Inspections in our Boston office.

Mr. Chairman, the IRB system, which has provided important protections for human subjects for so many years, needs to be reformed. While I bring you no evidence of widespread harm to research subjects at this time, I do feel obligated to call your attention to weaknesses inherent in the system that was designed to protect them.

Research and medicine have changed dramatically in the past decade. However, our system for ensuring human-subject protections has not kept pace with these changes. Its shortcomings could become more apparent and significant in light of future developments. These include plans to increase the Federal investment in cancer and other biomedical research and a number of recent proposals recommending greater responsibilities for IRBs in the areas of genetics and patient confidentiality.

My testimony is based on more than a year of inquiry into the work of IRBs that we have just completed and on an earlier study performed by our office. Today we are releasing four reports that describe the results of our recent work. Our total effort reveals a brittle system

and even a few cracks. I call these to your attention now in the hopes of preventing more serious problems in the future.

### **Background on Our Inquiry**

We initiated the broad, systemic review in response to concerns raised in a prior Office of Inspector General study. In that study, we examined clinical trials involving four investigational medical devices, and, in each case, discovered limitations related to IRB review. These concerned serious matters such as the implantation of a device in three times the number of human subjects specified in the IRB-approved research protocol, the initiation of a research effort without the changes called for in the informed consent document, and the continuation of a research project for six weeks beyond when the IRB had suspended it.

We were also aware of concerns about the IRB system raised by others. For instance, in its 1995 report, the Advisory Committee on Human Radiation Experiments questioned the adequacy of the IRB review process and the effectiveness of Federal oversight. In that same year, the General Accounting Office issued a report identifying numerous factors inhibiting IRB performance.

In our most recent inquiry, we conducted a broad-based analysis of the IRB system in order to

gain an in-depth understanding of (1) the challenges facing IRBs and (2) how the IRBs and the

Federal government were meeting these challenges. Toward that end, we developed a

multi-faceted methodology drawing on many sources. These included analyses of Federal

records; an extensive literature review; site visits to IRBs in 6 academic health centers;

additional site visits accompanying FDA inspectors; a survey on the electronic e-mail forum for

those associated with IRBs; and the systematic gathering of data from representatives of about

**75 IRBs.** 

**IRB Role: Trust but Verify** 

The IRB review system is rooted in trust. IRBs work closely and collaboratively with

researchers, assuming the best of intentions on their part. This is one of the traditional

strengths of the system.

At the same time, IRBs have important responsibilities and authorities for verifying that the

intended human-subject protections are, in fact, being provided. In the 1970s, the national

commission whose work established the foundation for Federal IRB regulations elaborated at

some length on the kind of verification efforts that IRBs might undertake. The Federal

regulations established in the 1970s and 1980s recognized the importance of such verification

by giving IRBs the authority "to observe or have a third party observe the consent process and

**Human Resources Subcommittee House Government Reform and Oversight Committee**  the research." Further, it required IRBs to conduct continuing reviews of approved research "at intervals appropriate to the degree of risk, but not less than once a year." The National Institutes of Health has informed IRBs that these reviews must be "substantive and

meaningful."

Other groups such as clinical audit teams, clinical trials coordinators and research sponsors

themselves have responsibilities in overseeing the research process. However, IRBs are the

sole bodies whose central mission is the protection of human subjects. This fact emphasizes

the importance of IRBs' role in verification. (For further background information on IRBs, see

the primer attached at the end.)

**MAJOR FINDINGS** 

Our overriding finding is that the system of protections that has been so carefully developed

over the years is in need of reform. We base this conclusion on six main findings that we

present below.

1. IRBs Face Major Changes in the Research Environment.

As I mentioned, Federal IRB regulations were established during the 1970s and early 1980s.

At that time, most human-subjects research took place under government funding in a

university teaching hospital with established controls. The research itself was most often carried out by a single investigator with a small cohort of subjects at a single site. There was a considerable awareness of the risks of participating in research in the wake of several highly-publicized incidents involving the abuse of human subjects. IRB workloads were more limited and allowed ample time for deliberations over proposals.

Times have changed over the past 20 years and the changes have significant implications for IRBs. Medical institutions and particularly academic medical centers, where a large portion of clinical research takes place, are subject to increasing cost pressures due to the rise of managed care and capitated payments. A greater proportion of research is funded by commercial sponsors. IRBs feel pressure to accommodate these sponsors who are looking for quick turnaround of their research and for whom time is money. Many research protocols are now multi-center trials involving thousands of subjects, numerous investigators and institutions spread out across the country or even the world. Each institution has little knowledge of what is occurring at other sites, if problems have arisen, or even if other IRBs have called for changes in the protocol. Advances in biomedical research in areas such as gene testing or gene therapy raise many new and difficult ethical issues. Patients and consumers now demand access to research trials in the hopes of some benefit or treatment for life-threatening illnesses. IRBs must consider and ensure the equitable recruitment of subjects and, more importantly, ensure that subjects understand the distinction between research and treatment.

### 2. IRBs Conduct Minimal Continuing Review of Approved Research.

The IRBs' ongoing review of research after it has begun can serve as an important safety net for human subjects. This safety net may be more important now as individuals who consent in writing to participate do not necessarily understand the implications of their decision to participate. The 1995 Advisory Commission on Human Radiation Experiments found in their interviews with actual research subjects that few realized they were participants in research and many had little understanding of the informed consent forms they signed.

However, continuing review has become a low priority at many IRBs. For example, at one meeting we observed, several annual reviews and amendments were approved within the last 15 minutes of a 2 ½ hour meeting. One IRB member told us that he reviews the continuing review summaries during the board meeting to see if a patient has died. If no patient has died, then he generally will not raise questions.

Continuing review is also limited to a paper-based review at most IRBs. Board members and officials we spoke with reported that they seldom left the board room to visit the research site. In addition, although many IRBs would like to, few oversee the consent process or solicit feedback from subjects. Research investigators are relied upon to provide timely, accurate reports to the IRB. Several IRB members we spoke with are uncomfortable with this degree of reliance on self-reported data and would like to do more continuing review.

Continuing review is further limited by the inadequate information IRBs receive from outside sources. There is little communication between the Data Safety Monitoring Boards, which are created by research sponsors to oversee many of the large-scale trials, and the IRB. The adverse-event reports that the IRBs receive from sponsors arrive without sufficient contextual information to make them meaningful. When FDA issues a warning letter to a clinical investigator, it typically does not inform the IRB. And, when a sponsor or investigator submits a research plan, it may not inform the IRB of any prior review of that plan by another IRB.

In an effort to improve continuing review, the National Institutes of Health (NIH) and their Office for Protection from Research Risks (OPRR) and the Food and Drug Administration (FDA) have issued interpretations of Federal requirements in the forms of Dear Colleague letters and Information Sheets. However, from the perspective of the IRBs, some of these have served only to reduce IRB flexibility and add to their burdens.

### 3. IRBs Review Too Much, Too Quickly, with Too Little Expertise.

IRBs across the country are inundated with protocols. We found average increases of 42 percent in initial reviews during the past 5 years at the sites we visited. Some of them are now reviewing more than 2,000 protocols annually. These IRBs are also being flooded with adverse-event reports from the multi-center trials they oversee. One IRB reported receiving an average of 200 such reports a month. These problems are not found only in large IRBs; even

smaller IRBs are suffering. Several small IRB representatives told us that while the number of proposals they review is substantially fewer than at the large institutions, they often have only one staff member who is responsible for coordinating all IRB activities.

The increased workload, coupled with resource constraints, causes problems for IRBs and threatens the adequacy of their reviews. In an effort to cope, many are forced to rely on a pre-assigned reviewer to examine and summarize research plans. In some IRBs, unless one of the assigned reviewers raises a question or concern about the research, the board engages in little or no discussion at its meeting. Some IRBs have been able to increase the length of their meetings, but many others are forced to squeeze more reviews into a fixed block of time.

Science is becoming increasingly complex and many IRBs find that they lack sufficient scientific expertise on their boards or staffs to adequately assess protocols. This is particularly evident for protocols involving advanced biomedical techniques--such as gene testing--that raise scientific issues as well as moral and ethical questions that may not be apparent to the untrained eye. From time to time, IRBs will use consultants to fill the gap, but this can be costly and can bog down an already overburdened review process.

### 4. Neither IRBs nor HHS Devote Much Emphasis to Evaluating IRB Effectiveness.

IRBs have little basis for knowing how well they are accomplishing their mission of protecting

human subjects. Illustratively, when we asked one dean of a medical school how he knows when the IRB is doing a good job, he replied, "when I don't hear about them." Seldom, we found, do the IRBs seek out feedback from human subjects or their families. Nor do they often examine the complaints that they do receive to determine if they reflect broader, system problems or inquire as to how well the informed consent process is actually working. Independent, outside parties conducting such evaluations are even less frequent.

Federal oversight does not compensate for these deficiencies as it, too, is not geared to evaluating effectiveness. The OPRR's oversight is limited almost entirely to an upfront assurance process. The assurance is a document stating an institution's commitment to adhere to Federal requirements and is considered by most IRB staff we spoke with to have little impact on IRB functioning. The OPRR generally goes on-site only in instances of alleged breakdowns in IRB protections. Some of their reviews represent the most probing and results-focused inquires we have found of IRB performance, resulting in strong recommendations to the IRBs. But because of resource shortages, they are infrequent.

Between April 1997 and May 1998, OPRR conducted only one for-cause visit.

The FDA oversight involves a more frequent on-site presence. However, their visits focus almost entirely on IRB compliance with the procedural requirements set forth in Federal regulations- such as attendance at review meetings, completeness of minutes, and a review of the informed consent document. Such matters can be important indicators of performance, but

they give FDA little direct feedback on the actual effectiveness of IRBs. For instance, in an information letter to IRBs, FDA requires IRBs to make certain that individuals understand what they are consenting to when they agree to participate in a research effort. Yet, FDA's inspection process does not extend beyond determining that informed consent forms contain all the appropriate elements and that they have been reviewed by the IRB.

### 5. IRBs Face Conflicts that Threaten Their Independence.

In fulfilling their mission of protecting human subjects, IRBs must keep the interests of its subjects central. But, we found that many IRBs we spoke with face conflicts that could lessen their objectivity.

Clinical research, particularly from commercial sponsors, is an important source of revenue and/or prestige for most institutions. For example, at one of the academic medical sites we visited, about 25 percent of the operating budget (nearly \$200 million) derives from research activities. We found several examples of hospital IRBs that were housed in offices of grants and contracts or of clinical research programs, the very offices geared to bring in research dollars. Independent IRBs, which review primarily commercial research, are subject to similar pressures as several are owned by contract research organizations. Others may have

equity-owners as board members reviewing protocols. Such organizational placements, while not necessarily representing a conflict, certainly can accentuate pressures on IRBs to accommodate financial interests.

An important counterbalance to these sorts of pressures is the perspectives of certain IRB members whose concerns are primarily in nonscientific areas or who are not otherwise affiliated with the institution. However, Federal regulations require only one of each. We found few such "outside" members on the boards. It is not unusual for an IRB of 15 to 20 or more members to include only one or two noninstitutional members.

# 6. IRBs and Their Institutions Provide Little Training for Investigators and Board Members.

The review process can involve complicated ethical issues and scientific questions. Because of this, the education of board members, particularly "outside" members, is important. An understanding of these issues is also essential for research investigators who, themselves, initiate the informed consent process and interact directly with research subjects.

Nationally, in the context of the numbers of research investigators and the complexity of the ethical issues, such efforts are minimal. IRBs face significant obstacles which include not only insufficient resources, but the reluctance of many investigators to participate in training

sessions. For new IRB members, their orientation to the role is seldom much more than a stack of materials to read and on-the-job learning.

### RECOMMENDATIONS

We found the stresses on the IRB system to be significant enough for us to make a number of strong recommendations to NIH/OPRR and FDA. The thrust of our recommendations is for a more streamlined approach to providing human-subject protections, both at the local and Federal levels. At the same time, we call for a greater emphasis on accountability, performance, and results. Our recommendations include a number of actions, many of which, in the near-term, could help to address the vulnerabilities in the system. These are, among others:

### ■ Grant IRBs Greater Flexibility but Hold them More Accountable for Results

If IRBs are to meet the significant challenges facing them in the years ahead, they must be relieved of unnecessary burdens. Thus, we call for eliminating, or at least loosening, a number of the procedural requirements that Federal regulations currently impose on IRBs. An example of this is the requirement that IRBs conduct full, annual reviews for all research plans, regardless of the level of risk the plan poses to human subjects. The IRBs would enhance their efficiency, and thus their effectiveness, if they could be more strategic in how they use their limited time and resources. This would allow them to concentrate on those research plans

involving substantial risks to human subjects. We expect that by giving IRBs greater flexibility we will nourish the creativity and innovation illustrated in our report on promising approaches.

But a quid pro quo for allowing IRBs greater flexibility is an increased emphasis on accountability. This accountability must be achieved in two basic ways. First, we recommend that all IRBs under NIH/OPRR's and FDA's purview undergo performance-focused evaluations to assess their effectiveness in achieving their core mission. The evaluation results should be made available to the public. Second, we recommend that there be more extensive representation on IRBs of nonscientific and noninstitutional members. The current policy, which requires that there be one noninstitutional and one nonscientific member, does not provide an adequate measure of public accountability.

### ■ Reengineer the Federal Oversight Process

As it now functions, the Federal oversight of IRBs is not equipped to respond effectively to the issues we present in this testimony. We call for changes in the way that NIH/OPRR and FDA carry out their oversight responsibilities. We suggest reorienting the NIH/OPRR assurance process so that it rests essentially on an institutional attestation to conform to the IRB requirements set forth in Federal regulations. This attestation could be provided in a brief statement referencing the pertinent regulations. As a result, the scarce OPRR resources that are now devoted to reviewing and negotiating assurances could be freed up to conduct periodic

performance-based reviews and to provide education for investigators and IRB members. We also suggest that FDA search for ways of revamping its inspections, so that they focus less on narrow compliance matters and more on performance issues.

We particularly urge that FDA and NIH/OPRR incorporate into their oversight efforts specific lines of inquiry to determine how well IRBs are actually protecting human subjects. This would call for examining matters such as how the processes of recruiting, selecting, and gaining informed consent from human subjects actually work. It would also call for addressing verification effort to make sure that research plans are in fact submitted for review and that approved plans do not stray off course. The FDA and NIH/OPRR could enhance a performance focus by finding ways in which experienced IRB members and staff could play some on-site role in reviewing IRB performance.

### ■ Strengthen Continuing Protections for Research Subjects

The IRBs need to be more aware of what is actually happening at the research sites under their jurisdiction. They need to move beyond reliance on a signed informed consent document to ensure the integrity of the consent process itself. In the current system, IRBs have no way of knowing whether those participating in research truly understand that they are research subjects, and that there may be risks associated with their participation. Further, IRBs should find mechanisms to assure themselves that the research under their purview is being conducted

as planned. As we reported in our prior OIG work, the information provided to IRBs is not always accurate. In making this recommendation we acknowledge that trust is an important element to the system; but we also feel that IRBs have a vital role in verifying the information presented to them.

Certainly, increased flexibility will help ease the burden on IRBs and will allow them to concentrate their time and resources on high-risk research. But if they are to conduct meaningful reviews of approved research, they need to receive continuous feedback from the various other players involved in overseeing research. Key among these are the Data Safety Monitoring Boards that oversee many of the large-scale trials. The role of these boards is to review the continued safety and efficacy of trials; yet rarely do they provide IRBs with meaningful and timely feedback. Doing so would not only enhance the efficiency of review but would allow IRBs to focus on what they know best, *i.e.*, the continued applicability of the research plan to the local environment. To complete the information loop, the FDA needs to provide IRBs with feedback on actions it takes against investigators that are engaged in research under their purview.

### ■ Enhance Education for Research Investigators and IRB Board Members

In the final analysis, the most important continuing protection for human subjects is the presence of well-trained and sensitized investigators. Such research investigators can also

serve to minimize the need for regulatory intervention, be it by the Federal government or by IRBs themselves.

The NIH is well positioned to assume a leading role here since it funds a significant portion of the biomedical and behavioral research in the country. It should require that institutions which receive funds for human-subject research under the Public Health Service Act have a program to educate their investigators about human-subject protections. Simultaneously, investigators who receive money under this program should be required to provide a written attestation of their familiarity with, and commitment to upholding, Federal policies concerning the protection of human subjects. As identified in our report on promising approaches, a number of institutions have, of their own accord, begun to initiate educational programs for investigators. The Federal government should continue to foster these efforts by establishing model curricula, developing basic educational materials, and continuing to sponsor symposia and conferences.

Finally, IRBs should be required to provide an orientation program for new members and a continuing education program for all members. This would be especially relevant for noninstitutional and nonscientific members. Such a program should help to bring them up to a level where they can fully and actively participate on the IRBs to which they belong.

### CONCLUSION

In closing, Mr. Chairman, I would like to underscore that we do not document, nor do we suggest that, widespread harm is being done to human subjects. The current system of protections is supported by many conscientious researchers committed to protecting human subjects and by many dedicated IRB members and staff doing their best under trying circumstances.

But, I must reiterate our warning signal-- that the effectiveness of the current system of human-subject protections is in need of reform. IRBs are struggling under intense workload and resource constraints. This situation will only intensify if funding for research is increased and if IRBs are expected to take on additional responsibilities. We cannot afford to wait any longer to act. It is time for reform.

Thank you for the opportunity to testify on this most important topic. At this time, I would be happy to answer any questions which you or the other members of the Subcommittee may have.

### INSTITUTIONAL REVIEW BOARDS: THE BASICS

### What Do They Do?

The responsibilities of IRBs fall into two main categories: initial review and continuing review of research involving human subjects.

**Initial Review:** IRBs review and approve a research plan before the research is carried out. This review encompasses the research protocol, the informed consent document to be signed by subjects, any advertisements to be used in recruiting subjects, and other relevant documents. In carrying out this review, the boards seek to ensure any risks subjects may incur are warranted in relation to the anticipated benefits, that informed consent documents clearly convey the risks and the true nature of research, advertisements are not misleading, and the selection of subjects is equitable and justified. IRBs focus much attention on the informed consent document as it is the vehicle for providing information to potential research subjects.

**Continuing Review:** The continuing review process is multifaceted and includes required reviews "at an interval appropriate to the degree of risk but not less than once per year." In addition to this continuing review, study amendments and reports of unexpected adverse experiences by subjects are received periodically and reviewed to ensure that the risk-benefit ratio of the research has not changed and remains acceptable.

### Why Were They Established?

As public awareness and concern about the treatment of human subjects in research increased, the need for additional review mechanisms was evident. These concerns grew from stories of the abuse of subjects during the World War II trials at Nuremberg, the promotional distribution of thalidomide resulting in numerous children born with birth defects, the administration of cancer cells to chronically ill and senile patients at a hospital in New York, and others. A 1966 article by Henry Beecher brought prominent attention to human research abuses in medical schools and hospitals citing 22 cases involving highly questionable ethics. The formal requirements for the establishment of IRBs were outlined in regulations stemming from the National Research Act of 1974 and in FDA regulations issued in 1981.

### Where Are They Located?

An estimated 3,000-5,000 IRBs can be found across the country. They are most commonly associated with hospitals and academic centers. Boards also exist in managed-care organizations, government agencies (such as the National Institutes of Health, the Centers for Disease Control, and State governments), or as for-profit entities that are independent of the institutions in which the research takes place.

### How Are They Organized?

Federal regulations require that boards have at least five members with varying backgrounds. At least one member must have primarily scientific interests, one must have primarily nonscientific interests, and one must be otherwise unaffiliated with the institution in which the IRB resides. A quorum, with at least one member whose interests are primarily nonscientific present, is needed for voting.

### How Does the Department of Health and Human Services (HHS) Oversee Them?

Two agencies within HHS share responsibility for IRB oversight: the Office for Protection from Research Risks (OPRR) in NIH and the FDA. The OPRR's main tool for oversight is the assurance document. Any institution that intends to conduct HHS-funded research must have an assurance on file with OPRR. The assurance is a written statement of an institution's requirements and procedures for its IRB and human subject protections. Institutions conducting multiple HHS-supported studies can apply for a multiple project assurance (MPA) which can be renewed every five years. Institutions with smaller HHS-funded workloads, however, use a single project assurance (SPA) for each such project it conducts. The OPRR also conducts a small number of site-visits. The FDA's main mechanism for IRB oversight is the inspection process. The FDA also inspects research sponsors and scientists (known as research investigators).